15. (Original) The method of claim 2, wherein the method comprises detecting the presence or absence of a mutation associated with impaired replication capacity at at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 amino acid positions.

16. (Original) The method of claim 15, wherein the method comprises detecting the presence or absence of a mutation associated with impaired replication capacity at amino acid positions 106 and 181; 103 and 190; 103 and 236; 181 and 236; 103 and 188; 103 and 181; 100 and 103; or 98 and 181.

17. (Previously presented) The method of claim 15, wherein the method comprises detecting the presence or absence of a mutation associated with impaired replication capacity selected from the group consisting of: V106A and Y181C; K103N and G109S; K103N and G190A; K103N and Y181C; K103N and Y188L; L100I and K103N; and Y181C and A98G.

18. (Original) The method of claim 15, wherein the method comprises detecting the presence or absence of a mutation associated with impaired replication capacity at amino acid positions 103, 181 and 236; 100, 103, and 190; or 103, 181 and 225.

19. (Previously presented) The method of claim 15, wherein the method comprises detecting the presence or absence of a mutation associated with impaired replication capacity selected from the group consisting of: L100I, K103N and G190S; and K103N, Y181C and P225H.

20. (Cancelled).

REMARKS

This amendment is in response to the non-final Office Action mailed May 11, 2005. Previously, Claims 1-19 were pending. Claims 1, 2, 5, and 6 have been amended. After entry of the instant amendment, Claims 1-19 will be pending and under consideration.

I. THE AMENDMENTS TO THE CLAIMS

Claims 1, 2, 5, and 6 have been amended to delete the recitation of position 103 and the specific mutation K103N. Applicants amend the claims solely to expedite prosecution of the present application and expressly reserve the right to present the cancelled subject matter in one or more division, continuation, or continuation-in-part applications. The amendments to such claims are fully supported by the application as filed. Specific support may be found, for example, in Claims 1, 2, 5, and 6 as originally filed.

In support of Applicants' contention that the larger groups of secondary mutations recited by the as-filed claims provide adequate description for the claims presented in the instant amendment, Applicants respectfully invite the PTO's attention to M.P.E.P. § 2173.05(i). Here, the M.P.E.P. explains that "[i]f alternative elements are positively recited in the specification, they may be explicitly excluded in the claims." *See* M.P.E.P. § 2173.05(i). The legal basis for this rule is found in *In re Johnson* 558 F.2d 1008, 194 U.S.P.Q. 187 (C.C.P.A. 1977). In *In re Johnson*, the Applicants described a genus of chemical compounds in the application as filed, then claimed a subgenus of the compounds that lacked word-for-word support in the application as filed. The Court of Customs and Patent Appeals held that "the specification, having described the whole [genus], necessarily described the [subgenus] remaining." *See In re Johnson* 558 F.2d 1008, 1019, 194 U.S.P.Q. 187, 196 (C.C.P.A. 1977). Thus, Applicants respectfully submit that *In re Johnson* and M.P.E.P. § 2173.05(i) show that the larger groups of secondary mutations described by the application as filed support the smaller groups of secondary mutations recited by Claims 2 and 6 as presented in the instant amendment.

Accordingly, the amendments do not introduce any new matter and are fully supported by the instant specification and the claims as originally filed. Entry and consideration of the amendments is therefore respectfully requested pursuant to 37 C.F.R. § 1.1411. No amendment fee is believed to be due.

II. THE REJECTION OF CLAIMS 1-19 UNDER 35 U.S.C. § 102(b)

Claims 1-9, 11 and 12 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Nijhuis *et al.*, *Current Opinion in Infectious Diseases*, 2001, 14:23-28 ("Nijhuis *et al.*"). In response, Applicants respectfully submit that Nijhuis *et al.* does not teach each and every element of claims 1-9, 11, and 12 as presently pending.

A. The Legal Standard

The standard governing anticipation under 35 U.S.C. § 102 requires strict identity. *See* M.P.E.P. § 2131. Thus, "for a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." *See In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Anticipation is not shown even when the differences between the claims and the cited reference are allegedly "insubstantial" and any missing elements could be supplied by the knowledge of one skilled in the art. *See Structural Rubber Prod. Co. v. Park Rubber Co.*, 223 U.S.P.Q. 1264 (Fed. Cir. 1984). Furthermore, in *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225

U.S.P.Q. 253 (Fed. Cir. 1985), the Federal Circuit explained that even if the prior art teaches "substantially the same thing" as the claimed invention, the reference still cannot anticipate the invention. Thus, a cited reference must describe each and every claim limitation in order to anticipate the invention as claimed.

B. Nihjuis *et al.* Does Not Teach Each and Every Element of Claims 1-9, 11 and 12

Without acquiescing to the propriety of this rejection, and solely to expedite prosecution of this application, Applicants have amended Claims 1, 2, 5, and 6. These amendments have rendered moot this rejection as to Claims 1-9. Furthermore, Applicants respectfully submit that Nijhuis *et al.* does not teach each and every element of Claims 11 and 12 and therefore that respectfully submit that Nijhuis *et al.* cannot anticipate such claims.

In particular, Nijhaus *et al.* cannot anticipate Claims 11 and 12 as it fails to teach the effects of *either* the P236L *or* the K103N mutation in combination with any other mutation affecting viral replication capacity. Nijhaus *et al.* does teach the effects on replication capacity of mutation combinations associated with resistance to protease inhibitors (Table 2) and to nucleoside reverse transcriptase inhibitors (Table 1), but nowhere does Nijhaus *et al.* teach, either explicitly or implicitly, the potential effects that the recited combinations of mutations, including combinations comprising mutations in residue 236 or 103, might have on replication capacity. As such, Nijhuis *et al.* does not teach, for example, the effects of mutations at both position 103 *and* 236 on replication capacity.

As Nijhaus *et al.* fails to teach anything about the effects of the recited mutations or mutation combinations on replication capacity, Nijhaus *et al.* cannot anticipate Applicants' methods for determining whether an HIV-1 is likely to have impaired replication capacity. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 1-9, 11 and 12 as anticipated under 35 U.S.C. § 102(b).

III. THE REJECTION OF CLAIMS 10 AND 13-19 UNDER 35 U.S.C. § 103

Claims 10 and 13-19 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Nijhuis *et al.*, *Current Opinion in Infectious Diseases*, 2001, 14:23-28 ("Nijhuis *et al.*") in view of Whitcomb *et al.*, WO 99/61658 ("Whitcomb"). Applicants respectfully traverse the rejection on the ground the Patent Office has not presented a *prima facie* case for obviousness in that the combined references do not teach or suggest each and every element of the invention as presently claimed and do not provide motivation to modify the teachings to obtain the missing elements.

A. The Legal Standard

To reject a claim under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention *prima facie* obvious.

To begin with, the prior art references cited by the PTO must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 51 U.S.P.Q.2d 1386 (Fed. Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a *prima facie* case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

B. The Cited References Fail to Establish a *Prima Facie* Case of Obviousness against Claims 10 and 13-19

In support of its rejection of Claims 10 and 13-19 under 35 U.S.C. § 103, the Patent Office alleges that Nijhaus *et al.* discloses the effects of antiretroviral resistance development on the fitness of the viral population and its clinical implications, and Whitcomb discloses means and methods for monitoring non-nucleoside reverse transcriptase anti-retroviral

(NNRTI) therapy, specifically HIV therapy. In view of these teachings, the Office argues that it would have been obvious to use the mutations taught by Whitcomb in Nijhaus *et al.*'s method. Therefore, the Patent Office contends that Claims 10 and 13-19 are *prima facie* obvious over Nijhaus *et al.* in view of Whitcomb.

Applicants respectfully submit that the Patent Office has failed to establish a *prima facie* case of obviousness of Claims 10 and 13-19. Neither Nijhaus *et al.* or Whitcomb, alone or in combination, teach or suggest that the recited combinations of mutations, including combinations comprising mutations at residue 236 or 103, may correlate with impaired viral replication capacity of an HIV-1 virus having these mutations in its reverse transcriptase. Since the references do not disclose the effects of the recited mutations on replication capacity, the combined disclosure of Nijhaus *et al.* and Whitcomb fails to teach or suggest either a method for determining whether an HIV-1 has an increased likelihood of having impaired replication capacity or a method for determining whether a subject has HIV-1 with an increased likelihood of having an impaired replication capacity, that comprises detecting a mutation or combination of mutations associated with impaired replication capacity of HIV-1 reverse transcriptase.

Moreover, whether a mutation associated with resistance will have an effect on replication capacity is not predictable. For example, Nijhaus *et al.* teaches that some mutations or combination of mutations associated with drug resistance either do not affect or even increase replication capacity (see Table 1). Thus, the mere fact that a mutation is associated with drug resistance does not imply that the mutation necessarily affects replication capacity. Therefore, Whitcomb's teaching that certain of the recited mutations and combinations of mutations are associated with NNRTI resistance cannot provide a reasonable expectation of successfully determining that an HIV-1 is likely to have impaired replication capacity by detecting the mutation or combination of mutations to an ordinarily-skilled artisan, since many resistance-associated mutations do not in fact affect replication capacity. Only impermissible hindsight based on Applicants' disclosure would support such a conclusion.

As shown above, neither Nijhaus *et al.* nor Whitcomb, alone or in combination, teaches or suggests a method for determining replication capacity that comprises detecting the recited combinations of mutations. Accordingly, Nijhaus *et al.* and Whitcomb, both alone and in combination, fail to teach or suggest each and every element of Claims 10 and 13-19. Further, the combination of Nijhuis *et al.* and Whitcomb do not provide a reasonable

expectation of successfully practicing the claimed methods. Therefore, Claims 10 and 13-19 are not obvious over Nijhaus *et al.* in view of Whitcomb. Accordingly, Applicants respectfully request that the rejection of Claims 10 and 13-19 under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. Applicants submit that Claims 1-19 satisfy all of the criteria for patentability and are in condition for allowance. The Examiner is invited to call the undersigned attorney at 650-739-3939 if a telephone call could help resolve any remaining items.

No fees, other than that for the Petition for Extension of Time, are believed due in connection with this response. However, pursuant to 37 C.F.R. §1.136 (a)(3), the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. §1.17 and all required extension of time fees, or credit any overpayment, to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: October 11, 2005

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